FASEB Summer Research Conference on "Transcription Regulation during Cell Growth, Differentiation, and Development"

Rationale and Justification

Over the past few years, it has become evident that transcriptional regulatory proteins play essential roles in a broad range of fundamental biological processes. For instance, many proteins that were purified or cloned as transcription factors have been found to be directly involved in recombination, DNA repair, the cell cycle and signal transduction. The purpose of this meeting is to bring scientists working in such critically important areas together with scientists who are leaders in the field of transcriptional regulation. This interchange will significantly enhance the future research progress of all of the participants, and will inspire the formation of key collaborative projects between scientists in different, yet interconnected fields of research.

Transcription governs a vast array of biological processes in organisms as diverse as viruses, prokaryotes and mammals. For example, transcription underlies critical aspects of cell behavior during development. Moreover, a wide range of highly specific differentiation programs are initiated and carried out through changes in gene transcription. In addition, the proliferation of normal and neoplastic cells is, to a large extent, subject to transcriptional control. Furthermore, many diseases and disorders, such as hypertension, cancer, neurological disorders, thallasemias, and birth defects, are related to abnormal gene regulation. Thus, a clear understanding of the fundamental mechanisms underlying transcription and of how these mechanisms are manifested temporally and spatially is of great importance.

Gene regulation is a major theme in molecular biology, and the last several years have been particularly fruitful in terms of our understanding of transcription at several levels. For example, important new information has emerged on the composition and function of the basal transcription machinery. Many of the components have been identified, and tentative functional roles have been assigned to many of the factors. At the same time, new insight has been gained into the structure and organization of sequence-specific binding regulators of transcription. A large number of these DNA-binding transcription factors have been identified, and their potential roles in gene-specific and tissue-specific gene expression have been analyzed at a variety of levels, which range from high resolution protein structure determination to the functional analysis of the factors in vivo by targeted deletion in transgenic mice. Research has also focused on how the factors involved in transcriptional activation (or repression) interface with the basal transcription machinery. This line of research has led to discovery of co-activators and mediators as well as a better understanding of interactions between transcription factors and the chromatin template.

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Not surprisingly, the advances in the area of basal and activated transcription have stimulated the analysis of complex biologic processes, such as embryology and developmental biology, cell cycle control, intra- and extra-cellular signaling systems, differentiation, and oncogenesis. Thus far, the bridging of these fields with transcriptional regulation has led to many important discoveries. For instance, our current understanding of heterodimerization and "networking" between different classes of transcription factors had emerged from studies of nuclear oncogenes, hormonal signalling, and transcription. Also, the identification of the homeobox and the characterization of homeodomain-containing proteins as transcription factors had resulted from the analysis of development and transcriptional regulation. Hence, there has been a rewarding and productive synergism between the study of basic transcriptional mechanisms and the analysis of the role of transcription in biological processes. This conference on "Transcription Regulation" for which we are requesting partial funding aims to increase that synergy and to extend new concepts in transcriptional regulation into novel areas.

Therefore, a major purpose of this FASEB conference is to provide a forum at which investigators who study such diverse process as development, the cell cycle, signal transduction, differentiation, and oncogenesis can productively interact with each other as well as with researchers who specialize in the analysis of fundamental aspects of basal and regulated transcription. This conference will stimulate the application of new concepts in transcription to biological problems of increasing complexity and human relevance, and will therefore lead to significant new insights into problems that are directly related to health.

Organization of the Conference:

The sessions have been designed to cover a broad range of topics with transcriptional regulation as the common theme. A list of the session titles and the invited speakers is provided on the following pages. We have elected to concentrate the first session of the conference on the molecular mechanism of transcription by RNA polymerase II. The first session (Sunday AM) entitled "Basal Transcriptional Mechanisms" deals with the components and regulation of the basal transcription complex in both yeast and mammalian cells.

The following session (Sunday PM) is focused on "Structure" and is devoted to the newest information on the three-dimensional structures of both basal and regulatory transcription factors. These results will increase our ability to predict the structures and functions of many other related factors and permit the design of rational mutagenesis and drug design strategies. Moreover, biophysicists provide a unique perspective into protein function. There will also be a reciprocal benefit to the structural biologists attending the meeting, as they will be able to gain a broader understanding of gene regulation and to find new subjects for analysis.

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The Monday AM session will focus on "Chromatin." This session will feature the rapid progress being made on the study of transcriptional regulation in the context of the native chromatin template. The topics will include the analysis of factors involved in the assembly and reconfiguration of nucleosome structure as well as the role of higher order chromatin structure in the regulation of gene expression. These talks will highlight the continuing convergence in the study of the trans-acting transcription factors and the structure and assembly of the native chromatin template.

One of the most exciting recent developments in transcription is the realization that transcriptional control proteins are also fundamentally involved in recombination and DNA repair. The session on Monday PM will bring together speakers that have been leaders in each of these areas. These individuals, coming from disciplines that seldom cross paths, such as immunology, transcription, and radiation research, will provide a unique mixing of expertise with transcription being the unifying theme.

A great deal of effort has been expended in defining the manner in which signal transduction pathways converge to regulate specific gene expression. One of the best understood systems is the steroid and glucocorticoid hormone receptors, which are themselves ligand-activated transcription factors. The Tuesday AM session is focused on the hormone receptors: their interactions with each other and with the basal transcription machinery, and the nature of their gene targets during mouse development. The following session (Tuesday PM), on "The Interface of Signaling Transduction and Transcription" is primarily concerned with the pathways by which several different cell surface receptors and extracellular ligands activate transcription. The Wednesday AM session on "Cell type determination" begins with a study using the power of Drosophila genetics to dissect the transcriptional control of pattern formation in embryogenesis and then moves into mouse developmental biology. Speakers here will describe the role of the myc proto-oncogene family of transcription factors in organ induction and the role of transcription studies in tissue culture and in simpler organisms. This is an excellent time to demonstrate progress in this area and to encourage new research.

The two sessions on Wednesday PM and Thursday AM will focus on cell proliferation: the role of transcription in cell cycle entry and exit through regulation of the expression of cell cycle modulators such as cyclins, cyclin dependent kinases, and rate-limiting components required for S phase. Specific attention will be paid to oncogenic transcription factors (myc, myb and jun/fos) and tumor suppressors (p53) involved in human and animal cancers. The recent realization that tumor suppression by RB might employ mechanisms that interact with chromatin will help unify this session with the one on chromatin.

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Conference Plan

We are requesting funds on a one-time basis to support a 5 day FASEB Summer Research Conference on "Transcription Regulation during Cell Growth, Differentiation, and Development" to be held at Snowmass, CO from August 10-15, 1996. The conference will comprise nine sessions with four or five speakers per session. Thirty-six speakers, who are leading investigators in the areas of the program, are confirmed participants in this meeting. Speakers were chosen by the two co-chairs in consultation with the session chairs. Funds are requested to provide partial support for the speakers with registration, lodging and meals for the five day periods at nominal costs as well as for round-trip economy class airfare. We are also requesting travel fellowships for 10 young investigators. These young scientists would be postdoctoral fellows or graduate students from the US who are planning to work in the areas covered by the conference. The conference will be advertised in widely read journals such as Nature, Science, Cell, Genes & Development, Journal of Experimental Medicine, Journal of Cell Physiology, and Journal of Cell Biology. We will also advertise in more specialized journals focusing on areas that are relevant to the conference: Neuron, Immunity, Blood, and Development. The remainder of the conference participants (up to a maximum of 200) will be selected from those responding to the advertisements based on short written abstracts of their work. Criteria for admission will be based on research areas and interests as well as the desire to have diversity in the background and expertise of the conference participants. When this meeting was previously held in August 1994, it was heavily oversubscribed because of the intrinsic importance of the subject material and the absence of other meetings that cover the same topical areas.

The conference will begin in the morning of Sunday August 10th and end at noon on Thursday August 15th, 1996. The meeting will have two three hour sessions per day with the exception of the final day. Participants including invited speakers are expected to attend the entire meeting. Each session will have four or five presentations of approximately 30 minutes with 10 minutes for questions and discussion. The chair for each session is the first speaker listed in the session on the following pages. Each chair will present a ten minute summary of their area emphasizing the context of the research to be presented. Speakers will also present a brief background to their talks and then concentrate on unpublished data. Particular mention will be given to conceptual and methodological advances. Presentations of exciting new research results may be added to the session as short talks at the discretion of the session chairs. In addition to the formal sessions, there will be two poster sessions scheduled in the afternoon to provide all conference participants with the opportunity to present their research findings at this meeting.

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The small size of the meeting and its location in a beautiful setting free of distractions will foster interactions among conference participants. Free time between the sessions, one central dining area where conferees will eat together and

the presentation of posters by meeting participants would also be expected to augment interactions. This should lead to dissemination of new ideas and the establishment of collaborations between laboratories.

A Note on Funding

Both of the conference co-organizers are acutely aware of the fact that budgetary constraints have negatively affected funding for many valuable research projects over the last several years. Under these conditions, it is reasonable to question whether meetings, such as that proposed here, are not simply luxuries whose funding only exacerbates an already bad situation for research grants. In preparing this proposal, the co-organizers have borne several considerations in mind. First, a conference such as this is a natural and necessary outgrowth of a productive scientific field. While dissemination of information through journal publications is of course absolutely necessary, it is nonetheless a slow and cumbersome process. Indeed, it is at conferences such as the one proposed here that new findings are first presented, argued over, modified and rapidly assimilated into the scientific community. It is at this type of conference that scientific excitement is generated, collaborations established, and ideas tested on colleagues. Second, the funds requested for this conference are relatively small compared to a standard research grant, especially given the scope and impact of the meeting. Third, this is a unique meeting. Although there are separate specialized conferences dealing with basic transcription, or nuclear oncogenes, or development etc., we are not aware of any other meeting during the coming year that attempts to place transcriptional regulation in the broader contexts of differentiation, development, and oncogenesis. In summary, we feel that the proposed conference is not a luxury, but rather a highly cost-effective and unique way to build on the results emerging from one of the most exciting fields in science.

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